

WE CLAIM:

E1 { 1. A method of modifying a polypeptide, comprising:  
a) identifying at least one immunodominant epitope in a polypeptide using an antibody or population of antibodies obtained from a naïve human or animal or population thereof; and  
b) modifying the immunodominant epitope to reduce an immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide.

Sub 1 2. A method according to claim 1 wherein the polypeptide is a recombinant polypeptide that has an amino acid sequence that is homologous to all or a part of a native sequence of an endogenous polypeptide in the animal.

3. A method according to claim 1, wherein the polypeptide is a recombinant polypeptide that has an amino acid sequence identical to all or part of a native sequence of an endogenous polypeptide in the animal.

E1 { 4. The method according to claim 1, wherein the polypeptide is selected from the group consisting of human thrombopoietin, growth hormones, cytokines, receptors, and humanized antibodies.

Sub 2 5. A method according to claim 1, wherein the animal is selected from the group consisting of humans, primates, cattle, pigs, poultry and mice.

E1 { 6. A method according to claim 1, wherein the modification is a deletion of at least one immunodominant epitope.

7. A method according to claim 1, wherein the modification is a modification of at least one amino acid in the immunodominant epitope by N-glycosylation or pegylation.

8. A method according to claim 1, wherein the modification is a mutation of one or more amino acids in at least one immunodominant epitope.

9. A method according to claim 1, wherein the polypeptide is produced in a non human source.

10. A method of modifying a therapeutic polypeptide, comprising:

- a) identifying at least one immunodominant epitope on a therapeutic polypeptide, wherein the immunodominant epitope is identified by binding to antibody or population of antibodies from a naïve human or animal and by binding to an antibody or population of antibodies from an animal or human dosed with the therapeutic polypeptide; and
- b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

11. A method of modifying a therapeutic polypeptide, comprising:

- a) identifying at least one epitope on a therapeutic polypeptide, wherein the epitope binds to an antibody or population of antibodies from a naïve human or animal and binds to an antibody or population of antibodies from an animal or human dosed with the therapeutic polypeptide;
- b) determining whether the epitope is an immunodominant epitope by using the antibody or population of antibodies from a naïve human or animal and by

using an antibody or population of antibodies from a human or animal dosed with the therapeutic polypeptide; and

c) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the polypeptide.

12. A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope on a therapeutic polypeptide by using an antibody or population of antibodies obtained from a naive human or animal or population thereof, wherein the antibody does not substantially inhibit a therapeutic activity of the therapeutic polypeptide; and

b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the polypeptide.

13. A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope of a therapeutic polypeptide by using an antibody or population of antibodies from a naive human or animal or population thereof,

b) selecting the immunodominant epitope that is not located in a region of the polypeptide providing a therapeutic activity of the polypeptide; and

c) modifying the selected immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

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14. A method of modifying a therapeutic polypeptide, comprising:
  - a) identifying at least one immunodominant epitope in a therapeutic polypeptide using an algorithm; and
  - b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.
15. A method according to claim 14, wherein identifying at least one immunodominant epitope comprises:
  - a) providing a data set of the therapeutic polypeptide;
  - b) analyzing the data set with an algorithm to identify at least one predicted epitope in the therapeutic polypeptide; and
  - c) determining whether the predicted epitope is in an immunodominant epitope by immunoreacting a peptide having the sequence of the predicted epitope with an antibody or population of antibodies specific for the therapeutic polypeptide from an animal or a population of animals.
16. A method according to claim 15, wherein the antibodies are from a naïve animal or population of animals.
17. A method according to claim 16, wherein the antibodies do not substantially inhibit a therapeutic activity of the polypeptide.
18. A method according to claim 15, wherein the therapeutic polypeptide is a recombinant polypeptide that is homologous to an endogenous polypeptide in the animal.

19. A method according to claim 15, wherein the data set is the linear amino acid sequence of the polypeptide in machine readable form.

20. A method according to claim 14, wherein the algorithm is an algorithm that predicts epitopes that bind to Class II major histocompatibility proteins.

21. A method according to claim 14, wherein the algorithm is implemented by a computer.

sub C5 22. A method for selecting at least one immunodominant epitope to be modified in a polypeptide, comprising:

a) identifying at least one epitope in the polypeptide recognized by an antibody or population of antibodies from a naïve human or animal population thereof and recognized by an antibody or population of antibodies from a human or animal or population thereof dosed with the polypeptide, wherein the polypeptide is homologous to an endogenous polypeptide in the human or animal; and

b) selecting at least one of the identified epitopes by determining whether the identified epitope is in at least one immunodominant epitope in the polypeptide.

23. A modified therapeutic polypeptide having a modification only in an immunodominant epitope, wherein the modification reduces the immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide.

sub B1 24. A modified human recombinant thrombopoietin comprising an amino acid sequence of amino acids 1 to 311 of Figure 7.

25. A modified human recombinant thrombopoietin comprising an amino acid sequence of amino acids 1 to 317 of Figure 7.

26. A modified polypeptide according to claim 23, wherein the polypeptide is human recombinant thrombopoietin with at least one modification of amino acids 312 to 332.

27. A modified polypeptide according to claim 26, wherein the modification is in amino acids 318 to 332.

28. A modified polypeptide according to claim 23, wherein the modification is a deletion, substitution or insertion of at least one amino acid in the immunodominant epitope.

29. A modified polypeptide according to claim 23, wherein the modification is a chemical modification of at least one amino acid in the immunodominant epitope, wherein the chemical modification is N-glycosylation or pegylation.

30. A method of modifying a nucleic acid encoding a modified polypeptide comprising:

- a) identifying at least one immunodominant epitope in the polypeptide;
- b) providing an isolated nucleic acid sequence encoding the polypeptide; and
- c) modifying the isolated nucleic acid to encode a modified polypeptide wherein the modified polypeptide has at least one change in the immunodominant epitope and wherein the change reduces an immune response to the polypeptide while still retaining a substantial therapeutic activity of the polypeptide.

31. The method according to claim 30, further comprising transforming a host cell with the modified isolated nucleic acid.

(32.) An isolated nucleic acid encoding a modified human thrombopoietin whereby the modified thrombopoietin has a modification only of amino acids 312 to 332.

33. A pharmaceutical composition comprising the modified polypeptide of claim 23 and a pharmaceutically acceptable carrier.

(34.) A method of treating thrombocytopenia by administering a modified recombinant human thrombopoietin, wherein the human recombinant thrombopoietin has at least one modification only of amino acids 312-332, wherein the modification reduces an immune response to human thrombopoietin while still retaining a substantial therapeutic activity of human thrombopoietin.

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